Compliance and Surveillance

Compliance Inspection Program

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Surveillance and Enforcement of CGMPs—Basic Information

- Annual site registration and product listing
- Routine CGMP inspection
- Preapproval inspection
- Quality problem reporting
  - Consumer complaint system; trade complaints
  - Adverse event reporting (MedWatch)
  - Recalls and defect reports from manufacturers
    - 21 CFR Part 7; see also guidelines on managing recalls
    - Obligatory “Field Alert Report”: *21 CFR Part 314.81*
      - failure to meet spec after distribution

Registration/Listing for PET

- All PET drug producers are required ***now*** to register and products are to be listed (except IND/RDRC)
  - Drug establishment registration and drug listing information is to be submitted electronically
  - DRLS PET Business Code for registering is: **C91403**
  - Website for information:
    - http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/DrugRegistrationandListing/default.htm

Drug Inspection Program: General

- Preapproval Inspection (PAI)
  - New site; new molecular entity; new sponsor; last CGMP inspection >~2 yrs
  - Center or local office initiated 'for-cause'
- Routine CGMP (Surveillance) Inspection
  - 2-yr cycle; sites selected by CDER & district office
  - Audit to verify CGMP compliance
- 'For-Cause' (Compliance) Inspection
  - f/u past deficiencies
  - External complaint (e.g., from user, other)

Objectives of Preapproval Inspection Program

To verify and ensure:

- Readiness for production and CGMP adherence
- Conformance to application commitments
- Authenticity and accuracy of data in application

May include inspection of

- Product/process development activities/records
- Equipment/process qualification, procedures, and records (batch, analytical, maintenance)
- Actual conditions and practices

PET Inspection Program: Current Status

- Current program status:
  - Relatively few sites this year; more in 2012+
  - Coverage of USP<823> or 21 CFR 212, as appropriate
  - Focus on sterility assurance
    - Procedures; simulations; technique; controls; maintenance; monitoring; cleaning
  - Assigned to more experienced drug investigators w/ PET training
- Training of PET inspection "team" members
  - Several sessions held to date
    - Includes both investigators & compliance officers
    - Focus on common processing/testing techniques and USP<823>
  - Larger event planned for later this year before 12/11
  - Challenge: distinguish PET from other sterile, injectable drug production

FDA Inspection Protocol

- Open inspection
  - Issue written Notice of Inspection (Form FDA 482)
  - Display credentials
  - Explain purpose and general ‘agenda’
- Perform inspection
  - Facility; material; equipment; records; personnel; product; practices
  - Possible daily summary of findings and changes to ‘agenda’
  - May comment on possible deficiencies when observed
- Close inspection:
  - Either issue written List of Inspectional Observations (Form FDA 483) or
  - No inspectional observations

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER [redacted]	DATE(S) OF INSPECTION 5/4 – 6/09
	FEI NUMBER
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED TO: [redacted]	
FIRM NAME [redacted]	STREET ADDRESS [redacted]
CITY, STATE AND ZIP CODE [redacted]	TYPE OF ESTABLISHMENT INSPECTED [redacted]

DURING AN INSPECTION OF YOUR FIRM I (WE) OBSERVED:

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

1. Sodium Fluoride batch [redacted] which was utilized in the stability studies supporting DMF [redacted] failed the membrane filter integrity test (bubble point) on 2/27/08. According to SOP [redacted] the acceptance criteria is >46 psig. The batch record indicates a failing result of 4 psi. This failure to meet specifications is not documented in the DMF.

2. Review of the Daily Operations Checks for the time period of December 2003 – present revealed numerous instances in which the recorded temperatures for the main laboratory and incubator exceeded the acceptable temperature ranges as stated in SOP [redacted] and SOP [redacted]

For example:

In January 2004, the incubation conditions for sterility test samples of FTM exceeded the acceptable temperature range of 30 – 35 C on 22 of 25 days.

In April 2008, the incubation conditions for sterility test samples of TSB exceeded the acceptable temperature range of 20 – 25 C on 20 of 26 days.

Possible Inspection Outcomes

Scenario 1:

No inspectional observations form issued (Form FDA 483, Inspectional Observations):

- Likely no adverse administrative or regulatory outcome

Scenario 2:

Inspectional observations issued

- If deemed of lesser significance:
  - No adverse outcome if positive response from site
- If deemed of greater significance:
  - Letter (warning or untitled)
  - Application recommended for disapproval
  - When commercial product affected possible outcomes:
    - Seizure
    - Injunction
    - Application withdrawal
    - Prosecution; debarment of individuals for generic

Field office decision

Agency decision